explicit breast cancer efficacy claims about Evista. Those claims fall into the following two categories and are typified by the statements quoted below.

a. Claims that Evista has been *proven to reduce the risk of breast cancer*

• "I explained evista decreases risk of breast cancer drastically compared to placebo." (10/8/98-844401745)
• "[I] tell him that e reduces the incidence of newly diagnosed breast cancer ranging from 50 to 80%." (10/20/98-210000310)
• "[H]it him with strong evista message...he asked if we have a cancer indication or a treatment indication ...told him the indication are coming it's just a matter of time...but the data is there and is strong." (11/4/98-338007116)
• "Ev: he basically said he doesn't believe the claims Ev has made... w/ cancer (breast cancer reductions) . ..need to be confident in standing up for Ev and telling him these claims are proven not suspected." (11/16/98-348606679)
• "She mentioned that Evista doesn't reduce the risk of breast cancer [sic]. I sd well doctor that is not true any longer. I then went through the MORE data and Asco data."(11/17/98-657601659)
• "Promoted breast cancer prevention need to remind her next time."(11/24/98-807602090)
• "Told [Dr.] that all pm pts are right because evista. .. has been shown to reduce cancer risk." (12/4/98-615802967)
• "Evista 3 combined benefits for the prevention of all three diseases not just one."(12/4/98-736800257)
• "Told him new data on EV...now shown to reduce risk of newly diagnosed breast cancer vs placebo." (12/15/98-489006635)
• "[H]e asked does that mean you can be used for breast cancer-I said no we do not have breast cancer indication but by the fda allowing us to put this data in our pi they believe there is a defenite [sic] decrease risk."(1/11/99-848001303)
• "I told him to rest assure and to tell Pt.'s actually reducing the incidence of breast cancer." (1/20/99-848801004)
• "He said Evista will be huge once we can say for sure that it protects women against breast cancer. I said 'with all due respect, Dr. Dejarnatte, that's what the package insert now states with the change that took place in December." (1/25/99-761405939)
• "I told him now he can actually say with confidence that Evista actually reduces the incidence of breast cancer..." (1/26/99-848801056)
• "[P]oint out the fact that there's no 'up-in-the-air' w/ evista, because we know it reduces breast cancer, etc."(2/8/99-240003187)
***13** • "[Q]uick reminder evista builds bone, lowers lipids and reduces the risk for breast cancer...." (2/12/99-618492020)
• "Told her that EV is not a BC drug, but the BC prevention is an element of the combined benefits of the drug."(2/25/99-678008612)
• "Bottom line is why give women agent that will make them worry they could get breast cancer when can give an agent that can prevent it." (3/1/99-740210792)

Pl.'s Exh. 25 (Call Notes of Eli Lilly Representatives).

b. *Claims that Evista is proven equal or superior to Tamoxifen*

• "[E]vista 3 way-wanted to know re breast cancer data-told him the 60-80% reduction-he said what about tamox-said evista's data is better and doesn't increase risk for endometrium either." (10/5/98-578403397)
• "F [follow up]: Push tamoxifen vs evista-BC data doc needs to hear again and again-why even start pats on tamoxifen?"(10/15/98-623600314)
• "[H]e asked right away about BC, went into MORE and compared w/ Tamoxifen, we agreed that evista is a much better choice...." (11/3/98-244001904)
• "He then wanted to know if I was saying-replace Tamoxifen with Evista. I said well, no FDA approval, but most of the doctors are already doing that, what will you do? He said Tamoxifen rep already came to detail him. I said so far what you have is study on Tamox vs. placebo and Evista vs. placebo, although you can't really compare, Evista looks better and without the endo effects." (11/16/98-422406095)

• "evista-3 way combined benefit given, interested in the STAR study and the breast cancer prevention, mentioned the MORE study and that evista's reduction in incidence of newly diagnosed breast ca was greater than tamoxifen's."(11/23/98-921201870)
• "Asked if [STAR trial] will show Evista is better than Tamox. Told him already better-No endo. cancer."(12/14/98-248000538)
• "Informed him about 63% reduction of breast cancer among women who have high risk of breast cancer compared to [Tamoxifen.] He was pretty pleased with that."(12/17/98-888000151)
• "Shared with him the PI change. He also asked how that compares to Tamoxifen. Explained we are believed to build bone every bit as well, and we don't have the endometrial issues they have. Evista is clearly a better choice for many reasons." (1/8/99-587000147)
• "Evista first line ahead of tamox. for prevention." (1/12/99-281202408)
• "He talked to me about several women that the oncologists were switching from Tamoxifen to Evista. He asked me if this was ok in my opinion. I stressed breast cancer data again about reductions in pervasive type cancer and ert positive cancer. He said he guesses it makes sense but he'd be more comfortable with some studies. I started to tell him the lack of studies didn't slow him down from rxing ERT but I didn't. Maybe next time." (1/21/99-870608719)
• "Nolvadex rep had just left.....listened to her give entire tamox detail.....gave all sorts of figures on BC.....went right in and asked him..... .'Dr Bill, why and where would you ever use Tamox over Evista? ? ? ?' /..... said he wouldn't..... ....no reason to with the risks of endomet cancer, which of course she DID NOT mention." (2/17/99-360201058)

***14** Pl.'s Exh. 23 (Call Notes of Eli Lilly Representatives).

37. There are some call notes from Eli Lilly sales representatives that suggest that a very small number sales representatives have told doctors that Evista has been approved or indicated by the FDA for the prevention of breast cancer. *See* Pl .'s Ex. 24. However, many other call notes indicate that representatives have informed doctors that Evista is not indicated for the prevention of breast cancer. *See, e.g.,* Pl.'s Ex. 25 (call note from 1/11/99-848001303). Moreover, one of the verbatims that was given to sales representatives specifically instructed them to tell doctors that " Evista is not approved for the prevention of breast cancer."Pl.'s Exh. 15 at EV 2609 327. Thus there is insufficient evidence to conclude that Eli Lilly sales representatives have promoted Evista as approved or indicated by the FDA for the prevention of breast cancer.

38. The entries in which the two claims about Evista were made-that Evista has been proven to reduce the risk of breast cancer and that Evista is comparable or superior to tamoxifen for reduction of the risk of breast cancer-were written by more than 170 different representatives, or approximately 17 percent of Eli Lilly's general sales force. In addition to being largely reflective of the Eli Lilly scripts, the fact that representatives recorded these messages in the business records of the company confirm that they were not inadvertent or unauthorized. Indeed, as set forth below, Eli Lilly executives and Eli Lilly's verbatims confirm that the representatives are authorized to convey these messages.[FN6]In fact, at the hearing Eli Lilly conceded that its representatives are authorized to state that raloxifene has been established to reduce the risk of breast cancer. (Tr. dated June 24, 1999 at 69, 74.) The verbatims and testimony of Eli Lilly executives also confirm, however, that Eli Lilly sales representatives have not promoted Evista as having been approved or indicated by the FDA for the reduction of the risk of breast cancer. Thus the evidence establishes that two of the three contested statements have been made by Eli Lilly representatives.

FN6. Eli Lilly emphasized at the hearing that the nearly 600 offending call notes cited by Zeneca are purportedly just a small portion of the 1.8 million total call note entries concerning Evista compiled since January 1998. The only relevant period, however, is from October 1998 forward, since that is when Zeneca entered the breast cancer risk reduction market. In any event, that Zeneca did not offer more entries does not mean that Eli Lilly

representatives did not make these false claims on other occasions. In light of the detail scripts the representatives are required to follow, the testimony of Eli Lilly's executives, as well as the results of Eli Lilly's market research (described in more detail below), these hundreds of entries are appropriately representative of messages conveyed by Eli Lilly representatives on other occasions.

3. *Testimony by Eli Lilly's business executives*

39. The entries in the call notes are echoed by the testimony of three Eli Lilly executives: Denice Torres, Eli Lilly's Evista Brand leader; Newt Crenshaw, Eli Lilly's Vice President of Sales and Operations; and Garry Nicholson, Eli Lilly's Director of Oncology Business. The testimony of these executives supports the contention of Zeneca and Barr that two of the three alleged statements are being made and supports Eli Lilly's position that sales representatives have not been telling physicians that Evista has been approved or indicated by the FDA for reduction of the risk of breast cancer.

40. First, Ms. Torres testified that the "key breast cancer message" that Eli Lilly representatives should now communicate to physicians in response to unsolicited questions about Evista and breast cancer is that "in studies up to three years, Evista reduces the risk of breast cancer by greater than 50 percent," and that when a physician asks whether Evista reduces the risk of breast cancer, the representative should respond that "the data have shown and studies have shown that Evista reduces the incidence of breast cancer greater than 50 percent."Tr. at 863 (Torres). She also testified that the representatives are not directed to disclose any of the potential flaws in the MORE study or any other drawbacks which might bear on this conclusion, except for the fact that Evista is not indicated for breast cancer risk reduction. Tr. at 863-64 (Torres). Ms. Torres noted that responses by representatives to unsolicited questions from physicians are not isolated occurrences, since physicians are constantly asking a whole variety of questions depending on their level of interest. Tr. at 866 (Torres).

***15** 41. Ms. Torres likewise testified that if a physician asks what is meant by the phrase on the Evista label-"the effectiveness of Evista in reducing the risk of breast cancer has not yet been established "-an Eli Lilly rep is supposed to respond that "while Evista is not indicated for reduction in the risk of breast cancer there are data that demonstrate that Evista is effective in clinical studies in reducing the risk."Tr. at 216-17 (Torres). She also expressed satisfaction that the messages in question had been delivered by Eli Lilly representatives and that representatives continued to deliver them even after this litigation began. Tr. at 216, 874-75 (Torres).

42. Mr. Crenshaw, who is responsible for supervising Eli Lilly's primary care sales representatives, similarly testified that he would not be troubled if an Eli Lilly sales representative told a physician that the MORE data shows that raloxifene is effective in reducing the risk of breast cancer. Tr. at 186-87 (Crenshaw). Moreover, he testified that sales representatives are authorized to present data from the MORE trial without stating that "the effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established."Tr. at 177-78 (Crenshaw).

43. Finally, Mr. Nicholson testified that Eli Lilly at launch developed a program to detail oncologists concerning Evista during the first half of 1998. Tr. at 241-42 (Nicholson). The mere fact that Eli Lilly was detailing Evista to oncologists is itself telling, since Evista is not indicated for breast cancer treatment or prevention. Mr. Nicholson also noted that oncology representatives continue to respond to unsolicited questions from oncologists concerning Evista. Tr. at 262 (Nicholson).

44. Moreover, Mr. Nicholson testified that in their discussions with oncologists, Eli Lilly's oncology representatives are not prohibited from telling oncologists in response to unsolicited questions, that (i) the MORE study proves that Evista reduces the risk of breast cancer, (ii) Evista's reduction in the incidence of breast cancer is greater than tamoxifen's, (iii) the data on the Evista label demonstrates that Evista reduces the risk of breast cancer, and (iv) physicians may tell their patients that Evista reduces the risk of breast cancer. Tr. at 256-57, 259, 262, 265-66 (Nicholson).

Not Reported in F.Supp.2d, 1999 WL 509471 (S.D.N.Y.), 1999-2 Trade Cases P 72,603
(Cite as: Not Reported in F.Supp.2d)

4. *Eyewitness testimony*

45. Several Zeneca sales representatives and others have observed Eli Lilly sales representatives telling physicians and oncologists that Evista has been proven to prevent or reduce the incidence of breast cancer. For example, one Zeneca district manager testified that he overheard an Eli Lilly representative inform a physician that "the findings [of MORE] were there was a 77 percent reduction in breast cancer" for patients taking Evista. The Eli Lilly representative went on to note that "you're aware of the dangerous side effect profile of Tamoxifen."Tr. at 118 (McLellan). Another Zeneca representative overheard an Eli Lilly representative, in the presence of an Eli Lilly supervisor, tell a physician that "Evista would reduce the incidents [sic] of breast cancer."Tr. at 123 (Blair).

***16** 46. In addition, one Zeneca representative found an Evista patient brochure in a physician's office with a signed note from the Eli Lilly representative, which stated: "*New label* change includes the *Reduction* of Breast Cancer incidence-by 50%!" Tr. at 131-32 (Tirk) & Pl.'s Exh. 7 (emphasis in original). And a registered nurse working in the office of a well-known oncologist testified that an Eli Lilly representative told the nurse and the doctor that the MORE data which was soon to be released would "prove that the effectiveness of Evista had been established in breast cancer patients."Tr. at 272 (Landes). The doctor later told the nurse that the doctor "[didn't] like the way [Evista] was presented to us and I think that has been misleading."Tr. at 278 (Landes).

47. Finally, one Zeneca representative testified that last October in a doctor's office, and again at a physicians' conference in late March 1999-after this lawsuit had been filed-he observed Eli Lilly representatives repeatedly refer to clinical materials to convey the message that Evista has been shown to reduce the risk of breast cancer in women by 50 percent or greater. Tr. at 105-09, 110-11 (Centers).

5. *Eli Lilly's market research*

48. Market research commissioned by Eli Lilly likewise confirms that its representatives have been telling physicians that Evista has been proven to reduce the risk of breast cancer. As noted above, Eli Lilly's president acknowledged that, if the representatives were making breast cancer prevention claims, "you would expect" that fact to be reflected in the company's market research. Pl.'s Exh. 2; *see also* Tr. at 169 (Crenshaw).

49. According to the last Richard Day survey conducted in late November and early December 1998, physicians who were detailed by Eli Lilly representatives reported having received the following "main messages" based on their recent detail visit from an Evista sales representative:

- "prevention of breast cancer and osteoporosis"
- "decrease of breast cancer risk"
- "prevent breast cancer"
- "lowers risk of breast cancer"
- "shown to decrease risk of breast cancer"
- "Osteoporosis prevention and breasxt [sic] cancer prevention"
- "Decreases breast cancer"
- "Very effective prevention of breast cancer"
- "it reduces breast cancer risk"
- "new data has come to show it is effective in fighting breast cancer"
- "new indication of the reduction of bc"
- "the three-year study that's out now from the FDA that says that Evista lowers the risk of breast cancer" ; and
- "its [sic] shown to reduce the risk of breast cancer by 50 percent."

Pl.'s Exhs. 63 & 65; Tr. at 522, 524, 528-30 (Ross). Significantly, both the Project Manager for Richard Day and Eli Lilly's executives testified that they were satisfied with the methodology used by Richard Day and believed that the results were reliable. Tr. at 235-36 (Harenberg); Tr. at 526-27, 535 (Ross).

6. Eli Lilly's arguments with respect to two of the three *claims*

***17** 50. At trial, Eli Lilly did not meaningfully dispute that its sales representatives are making the claim that it has been established that Evista reduces the risk of breast cancer. In fact, counsel for Eli Lilly appeared to agree that Eli Lilly sales

representatives have been making that claim. (Tr. dated June 24, 1999 at 69, 74.) Instead, Eli Lilly contended that it is not making claims that Evista has been proven equivalent or superior to tamoxifen for reduction of risk of breast cancer or that Evista is approved by the FDA for the reduction of the risk of breast cancer. With respect to the claim that it has been established that Evista reduces the risk of breast cancer, Eli Lilly contended that, despite the contrary language in the Evista label, the statement is not literally false.

51. At trial, Eli Lilly attempted to undercut the accuracy of the call notes by relying on declarations from doctors who were detailed by certain of its representatives. The Court has considered these affidavits in light of the fact, as explained above, that the strict rules of evidence do not apply on a motion for a preliminary injunction. Nevertheless, the affidavits do not seriously compromise the persuasive evidence that two of the three contested statements are being made. That these statements are being made is supported by numerous sources in addition to the call notes themselves. Moreover, under the circumstances of this case, in which Zeneca challenges oral statements by Eli Lilly sales representatives, memory and credibility are critical. The absence of any opportunity for cross-examination renders these out-of-court statements of limited value. Eli Lilly had the opportunity to introduce the depositions of any of these doctors but did not. It is unlikely that a doctor would be able to recall what a particular sales representative did or did not say in a two or three minute conversation that took place several months ago. The affidavits do not purport to recount all of the relevant details of what was said in the conversations. Def.'s Exhs. T-4 through R-5. Under the circumstances, the contemporaneous call notes themselves, which fall under the well-recognized business records exception to the hearsay rule, are more persuasive evidence of what was said.

52. It is also significant that Eli Lilly has not made any representation that it will not make at least the claim that it has been established that Evista reduces the risk of breast cancer, nor has it undertaken to instruct its representatives not to make that statement. Indeed, Eli Lilly maintains that its representatives are authorized to state that it has been established that Evista reduces the risk of breast cancer.

53. In sum, for purposes of this preliminary injunction motion, Zeneca has met its burden of proving that Eli Lilly representatives are communicating the claims that Evista has been proven to reduce the risk of breast cancer and that Evista is comparable or superior to tamoxifen in reducing the risk of breast cancer.

E. Eli Lilly's claims about Evista are false

***18** 54. Eli Lilly's witnesses acknowledge that Evista is not indicated by the FDA for the reduction of the risk of breast cancer, Tr. at 199-200 (Crenshaw); Tr. at 265 (Nicholson), and thus that if its representatives are making that claim, it is false. However, the Court has found that there is insufficient evidence that Eli Lilly's representatives are making such a claim. Eli Lilly also concedes that Evista has not been tested against, much less proven comparable or superior to, tamoxifen. Tr. at 180, 208-09 (Crenshaw); Tr. at 740, 771, 786 (Cummings). That claim, too, is false and the evidence indicates that Eli Lilly's representatives are making that claim.

55. With respect to the remaining claim, Eli Lilly contended at the hearing that Evista has been proven to reduce the risk of breast cancer. As set forth below, however, the FDA, as well as numerous other experts in the field of clinical oncology, have reviewed the relevant data and reached the nearly unanimous conclusion that, while Eli Lilly's data is promising, it does not prove that Evista reduces the incidence of breast cancer. Given the state of the evidence, and particularly in view of the highly regulated nature of drugs and their indicated uses, at this time there is not sufficient evidence to conclude that raloxifene has been proven to reduce the risk of breast cancer. Thus the claim that raloxifene has been proven to reduce the risk of breast cancer is a false claim in light of current scientific evidence.

1. *The conclusions of the FDA*

56. By statute, the FDA is the agency that is responsible for determining the safety and efficacy of prescription drugs in this country. *See*21 U.S.C. § 393(b). The parties' experts and other witnesses testified, and the Court finds, that the FDA is a recognized authority and has expertise in assessing the results of clinical drug tests. Tr. at 372 (Lewis); Tr. at 427-29 (Carlson); Tr. at 740-41 (Cummings); Tr. at 1102 (Dere); Lippman Dep. Tr. at 84.

57. The FDA has reviewed all the breast cancer data from the MORE trial and has met with Eli Lilly's study investigators and scientists in response to Eli Lilly's request that the FDA evaluate whether the MORE data proves that Evista reduces the risk of breast cancer and would support such an indication for Evista. Based on its review, the FDA has repeatedly determined and communicated to Eli Lilly in Meeting Minutes that the MORE study does not and cannot prove that Evista reduces the risk of breast cancer. The Court finds the FDA's conclusions and reasoning highly persuasive.

58. One of the basic flaws cited by the FDA concerning Evista and breast cancer prevention is that the MORE study was intended as an osteoporosis study, not a breast cancer trial. To that end, the "primary objective[ ]" set forth in the MORE study protocol was "to establish the effects of long-term treatment ... with raloxifene... on the rate of new vertebral fractures in osteoporotic postmenopausal women ...." Def.'s Exh. P (Protocol H3S-MC-GGGK(e) [MORE study protocol]) at EV 013 837. Among the last of many secondary endpoints, the protocol instructed the investigators to gather data on the "risks of breast and endometrial cancer."*Id.* But the sole purpose of gathering this data was to find out whether long-term use of Evista was safe in the breast and would not increase a woman's risk of developing breast cancer. Tr. at 411-14 (Carlson); Tr. at 618-19, 622-25, 722-23, 728-29 (Cummings). The protocol was not designed, nor was the study intended, to determine if Evista would be efficacious in reducing the risk of breast cancer.

***19** 59. Women were not selected for the MORE study based on their risk of developing breast cancer , nor were they randomized between the raloxifene and the placebo arms of the MORE study based on breast cancer risk factors. Tr. at 730 (Cummings); Tr. at 1146-47 (Scott).

60. Months before the Evista launch, Eli Lilly itself anticipated this point and acknowledged the danger of relying on the MORE data to support a breast cancer risk reduction claim. For example, Eli Lilly's internal instructions to its oncology representatives concerning Evista declared:

Evista was not associated with an increased risk for breast cancer.... However, it is premature to draw conclusions about Evista as a cancer preventive agent. To do so would be a disservice to the millions of women who fear the disease.

Pl.'s Exh. 26 at EV 2446 40. Eli Lilly's Director of Oncology Business, Mr. Nicholson, testified that this statement is equally true today. Tr. at 250-51 (Nicholson).

61. The FDA's decision to allow Eli Lilly to include the interim data from MORE in the safety section of Evista's label does not, as Eli Lilly contends, demonstrate the FDA's acceptance of the MORE study as proof that Evista reduces the risk of breast cancer. In August 1997, in response to Eli Lilly's first such inquiry, the FDA advised Eli Lilly that the MORE data did not and probably never would support a breast cancer efficacy claim:

The data provided appear to be grossly insufficient to support a claim that raloxifene reduces breast cancer risk. Despite the summary nature of the information provided, it is unlikely that more information will improve the acceptability of the methodology or the credibility of the data used by the sponsor to conclude that raloxifene reduces the risk for breast cancer.

Pl.'s Exh. 38 (FDA Document-Center for Drug Evaluation and Research Approval Package-Evista, Medical Officer Consult dated Aug. 6, 1997) at EV 413 411. Among other criticisms, the FDA reviewer noted that the study lacked proper controls and that to support this claim Eli Lilly would need to develop a protocol in which "breast cancer incidence is a primary endpoint."*Id.*

62. In the fall of 1997, the FDA told Eli Lilly that " it is *not* acceptable to include language in the label that 'there was a statistically significant reduction in the frequency of newly diagnosed breast cancer in raloxifene-treated women compared to placebo"' because "[a]cceptance of this claim would effectively provide [Eli Lilly] with a second indication for raloxifene...." Pl.'s Exh. 40 (Breast Cancer Statement from FDA) at EV 651 1055; *see*

also Pl.'s Exh. 38. Later, in March of 1998, the FDA indicated that Eli Lilly could apply for a label change to reflect the interim data from the MORE trial. In doing so, however, the FDA's reviewer reiterated "[t]here are questions about the reliability of the [MORE] data"; that "[i]t is expected that it will not be possible to retrospectively obtain sufficient information to justify a claim related to breast cancer prevention"; and that if Eli Lilly were to reference the MORE study, the label would have to state that "[t]he effectiveness of raloxifene in reducing breast cancer has not been established." Pl.'s Exh. 41 (Medical Officer Review of Raloxifene Adjudication Data dated Mar. 2, 1998) at EV 415 2059.

***20** 63. In December 1998, the FDA approved a change in the safety section of Evista's label which allowed Eli Lilly to refer to the MORE breast cancer data as part of Evista's safety profile. In approving this limited change, however, the FDA again made clear that Eli Lilly could not use the MORE data to suggest that Evista has been shown to reduce the risk of breast cancer or that the drug has been approved for that purpose. Thus, Eli Lilly was able to report on the label the combined interim data from MORE and its other osteoporosis trials as follows:

Independent review has determined that 16 cases (raloxifene and placebo combined) represented newly-diagnosed invasive breast cancer. Among 7017 women randomized to raloxifene, there were 6 cases of invasive breast cancer per 14,605 person-years of follow-up (0.41 per 1000). Among 3368 women randomized to placebo there were 10 cases of invasive breast cancer per 6991 person-years of follow-up (1.43 per 1000).

But to warn physicians that this data was safety information only, the FDA required Eli Lilly to state expressly in the label that "[t]he effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established."Def.'s Exh. H at 8.

64. After the label change, in January 1999, Eli Lilly representatives attended a meeting at the FDA in an attempt to persuade the FDA's Oncology Division that more recent breast cancer data from the MORE trial-a total of 27 cases of invasive breast cancer on placebo and a total of 13 cases on raloxifene-proved that Evista reduces the risk of breast cancer and would support a contemplated supplemental new drug application ("sNDA") for an indication for the reduction of the risk of breast cancer. Prior to the meeting, Eli Lilly posed the following question to the FDA: "We believe the data presented in this briefing document provide compelling evidence that raloxifene reduces the incidence of breast cancer in post-menopausal women with osteoporosis.... Does the Agency concur ... ?"The FDA responded as follows:

We have concerns about the credibility of the finding (fewer cases on the raloxifene arms compared to the placebo arm). The following issues represent critical problems in the clinical trial design that probably cannot be addressed retrospectively.

Pl.'s Exh. 45 (Meeting Minutes for Jan. 28, 1999 Meeting, Questions for Discussion with FDA Response) at EV 2383 55. The FDA then proceeded to identify various flaws in the MORE trial, which went beyond the fact that "[b]reast cancer incidence was not prospectively defined as an endpoint."*See id.* at EV 2383 55-57.

65. Based on statements made by FDA officials at the January 1999 meeting, Eli Lilly's scientists concluded that "nothing could be done to salvage the MORE Study for a breast cancer indication."Tr. at 956, 959-60 (Eckert); Pl.'s Exh. 46 at EV 2386 1818. Shortly after the FDA issued these findings, Eli Lilly decided to terminate the MORE trial. Tr. at 962 (Eckert); Pl.'s Exh. 46 at EV 386 1818.

***21** 66. In response to this termination, the FDA urged Eli Lilly on March 11, 1999 to continue to follow up on the MORE patients, noting that such data "will provide important supportive information in conjunction with the STAR data for a sNDA submission for raloxifene to reduce the incidence of breast cancer."Pl.'s Exh. 46 at EV 2386 1820. Eli Lilly then proposed to the FDA that it would commence a "new" study called "Continuing Outcomes of Raloxifene" or CORE, using as many of the women enrolled in the MORE study who would agree to participate. Like MORE, CORE will continue to have both a raloxifene and a placebo arm and will last four years. Eli Lilly made substantial changes in the way the trial will be conducted. For example, the incidence of breast cancer is now the primary endpoint of the study; new study participants will be given a GAIL risk assessment; the appropriate statistical analysis for

the breast cancer data is set forth in the protocol; and the protocol requires annual breast physical examinations. Tr. at 751-53 (Cummings); Tr. at 938-40, 967-68 (Eckert).

67. Nonetheless, the FDA has since determined that MORE-even when coupled with the CORE extension-still will not prove that Evista reduces the risk of breast cancer. In early April, Eli Lilly submitted the CORE protocol to the FDA and posed the following question:

We believe that achievement of statistical significance with the stated endpoints in the enclosed proposed draft CORE protocol will confirm, along with the data provided to date from the 3-year MORE protocol, that Evista does reduce the incidence of invasive breast cancer after long term treatment in postmenopausal women with osteoporosis. Does the Agency concur with these conclusions?

Pl.'s Exh. 46 at EV 2386 1872. On April 16, 1999 the FDA responded as follows:

No, we do not.

The primary endpoint should be the occurrence of all invasive breast cancer.

Analyses that demonstrate long-term clinically and statistically significant differences between patients treated with raloxifene and placebo in the incidence of breast cancer will provide supportive evidence of efficacy. Data from a prospective randomized trial of raloxifene in which the reduction in the incidence of breast cancer is the primary endpoint will be needed, such as data from the STAR trial.

Pl.'s Exh. 47 (Facsimile from FDA to Eli Lilly dated Apr. 16, 1999) at EV 2736 000003.

68. The FDA recognized that the "CORE study will address some of the problems identified in the MORE study with respect to the breast cancer endpoint, such as poorly documented baseline status, short follow-up, and lack of consistent follow-up."FDA went on to explain, however, that " [d]espite these improvements, it is unlikely that data from [MORE] and CORE will be sufficient" to support an application for a breast cancer risk reduction indication.*Id.* at EV 2736 000002. Accordingly, the FDA told Eli Lilly that based solely on the combined data from MORE and CORE, it would not support a new drug application submission even for a limited indication "for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis."*Id.* at EV 2736 000003-04.

***22** 69. Representatives of Eli Lilly met again with the FDA on May 11, 1999. In the minutes of that meeting prepared by the FDA, which Eli Lilly received on June 4, 1999, the FDA reiterated that MORE and CORE cannot prove that Evista reduces the incidence of invasive breast cancer in postmenopausal osteoporotic women and told Eli Lilly once again that it would not support an sNDA based solely on the results of those studies. Specifically, Eli Lilly had asked the FDA:

We believe that achievement of statistical significance with the stated endpoints in the enclosed proposed draft CORE protocol will confirm, along with the data provided to date from the 3-year MORE protocol, that Evista does reduce the incidence of invasive breast cancer after long term treatment in postmenopausal women with osteoporosis. Does the Agency concur with these conclusions?

The FDA responded, consistent with its response on every previous occasion: "No, we do not." Def.'s Exh. K-9 (May 11, 1999 Meeting Minutes) at 3.

70. The FDA suggested several alternatives for Eli Lilly to consider, involving various combinations of MORE/CORE, the STAR trial and an Eli Lilly trial called RUTH, which is currently proposed to determine the cardiovascular effects of raloxifene. Alternatively, if Eli Lilly decided to pursue a " limited indication" for the reduction of the incidence of invasive breast cancer in postmenopausal women, "[i]t is possible that MORE/CORE plus RUTH will be sufficient to demonstrate a reduction in the incidence of invasive breast cancer" but the FDA suggested that Eli Lilly add breast cancer risk reduction as a primary or co-primary endpoint of the RUTH trial. Def.'s Exh. K-9 at EV 2736 000367; Tr. at 979-81 (Eckert). Thus, the FDA has made clear that MORE-even when coupled with the CORE extension-will not suffice as a basis for proving the efficacy of raloxifene in the reduction of risk of breast cancer.

71. None of the Evista trials Eli Lilly plans to conduct or participate in will be completed in the near future. CORE is supposed to last four years. RUTH is expected to last five years. Enrollment in STAR began just last month and the study will not be completed for at least five years. Tr. at 761

(Cummings); Tr. at 982 (Eckert). Thus, while the MORE results may be promising, it has not yet been shown to be sufficient proof that Evista reduces the risk of breast cancer.

3. Other experts have agreed that MORE does not *prove that Evista reduces the risk of breast cancer*

72. There is other support for the conclusion that it is premature to find that raloxifene reduces the risk of breast cancer.

73. During the testimony of the experts on both sides in this case, it became clear that the issue of whether the MORE trial has proven the efficacy of raloxifene in reducing the risk of breast cancer has been considered by several well-respected third-party organizations in the field of clinical oncology. Experts on both sides acknowledged that these organizations have determined that it is premature to conclude that Evista reduces the risk of breast cancer. Tr. at 331-34 (Lewis); Tr. at 430-41 (Carlson); Tr. at 668, 702-07 (Cummings).

***23** 74. In May of this year, a special committee of the American Society of Clinical Oncology ("ASCO "), issued a report based on its assessment of the propriety of using tamoxifen or raloxifene for reducing the risk of breast cancer. The Committee, comprised of leading experts in several fields, analyzed all research conducted on tamoxifen and raloxifene from 1990 through 1998. In response to the question, "Is there strong or credible evidence to conclude that raloxifene will reduce the risk of developing breast cancer" the Committee responded "it is premature to recommend raloxifene use to lower the risk of developing breast cancer outside of the clinical trial setting."Tr. at 430-33 (Carlson); Tr. at 668, 702 (Cummings).

75. Significantly, both parties' experts have testified that ASCO is the premier clinical oncology organization in the world. They also agreed that the conclusions of the ASCO committee, like any other ASCO publication, are entitled to great weight. Tr. at 292-93 (Lewis); Tr. at 394-95 (Carlson); Tr. at 705-07 (Cummings); Tr. at 1105 (Dere); Lippman Dep. Tr. at 85-87.

76. Similarly, a committee of the National Comprehensive Cancer Network ("NCCN"), a prestigious consortium of major cancer centers throughout the United States, has recently prepared a draft of breast cancer prevention guidelines. The draft guidelines conclude that "insufficient data are available to make definitive statements regarding the benefit or toxicity of raloxifene."Tr. at 434-35 (Carlson). The parties' experts agree that, like ASCO, NCCN is an expert body in the field of clinical oncology and that its guidelines are authoritative in the field. Tr. at 395-97 (Carlson); Lippman Dep. Tr. at 83-84.

77. At trial, Eli Lilly attempted to downplay the significance of the ASCO and NCCN guidelines-even though Eli Lilly's expert Dr. Steven Cummings served as a member of the ASCO Committee for a period of time, Tr. at 693-94, 697, 701 (Cummings)-because the organizations purportedly did not have the full data from the MORE study, which ran to a median of 40 months, or the recently published article in JAMA, written by doctors and other experts affiliated with the MORE study, which concluded that Evista reduces the risk of breast cancer in postmenopausal osteoporotic women after 40 months of treatment. However, there is no dispute that ASCO and NCCN had data through 33 months from the MORE study, Tr. at 708-09 (Cummings), a significant amount of data. In addition, the ASCO report made clear that the grounds for its conclusion were that "this study was designed as an osteoporosis trial; breast cancer risk was not specifically addressed at entry, nor was breast cancer development a primary outcome measure."The Committee also noted that the MORE finding was based on a small number of events. Tr. at 709 (Cummings). These deficiencies are not cured by an additional seven months of MORE data or by the publication of the JAMA article.

***24** 78. As for the NCCN, the expert who testified on behalf of Zeneca, Dr. Robert Carlson, is the Chairman of the Committee charged with drafting those guidelines. As set forth below, he is of the firm conclusion, even after having reviewed the 40-month data and the JAMA article, that raloxifene has not been proven to reduce the risk of breast cancer.

79. As indicated by the experts' testimony, two other organizations, the NCI and the NSABP-which are jointly sponsoring the upcoming STAR trial-have likewise made clear that the efficacy of

raloxifene in reducing the risk of breast cancer has not yet been proven. In the model consent form for the STAR study, which was prepared by scientists and about which both Zeneca and Eli Lilly had the opportunity to comment, participants in STAR are advised that the very purpose of the study is to try to find an answer to the following three questions:

• "Is raloxifene, also known by the trade name Evista, effective in reducing the incidence of breast cancer in women who are at increased risk for developing breast cancer?"

• "If it is effective, how does raloxifene compare to tamoxifen, also known as Nolvadex, in reducing the incidence of breast cancer?" and

• "How do the side effects (good and bad) of raloxifene and tamoxifen compare?"

Tr. at 324-27, 331-34, 357 (Lewis); 436-38 (Carlson); Pl.'s Exh. 34 (NSABP Protocol P-2, Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer) at 51. The model consent form also clearly states that *"[t]he FDA and the [Canadian Health Protection Branch] consider the use of raloxifene for reducing the risk of breast cancer to be experimental at this time."* Pl.'s Exh. 34 at 51 (emphasis added); Tr. at 333-34 (Lewis).

80. The Court was also persuaded by the testimony of two expert oncologists and one biostatistician offered by Zeneca. These witnesses-whom the Court finds to be both qualified and credible-cited numerous persuasive reasons why the data from the MORE trial, though encouraging, do not prove that Evista reduces the risk of breast cancer.

81. Dr. Robert Carlson is a professor of medicine and oncologist at Stanford University with extensive experience and expertise in the area of breast cancer treatment and research as well as the conduct and design of clinical trials. He was a principal investigator for the BCPT and is one of the investigators for the STAR trial. Tr. at 389-93 (Carlson). Having reviewed all of Eli Lilly's breast cancer data, including the results of the nine other osteoporosis studies conducted for Eli Lilly, Dr. Carlson testified that "the data is insufficient to conclude definitively that raloxifene decreases the incidence of breast cancer."Tr. at 398-402 (Carlson).

82. Dr. Carlson noted, first, the inconsistencies between the MORE results and those in the other nine Eli Lilly raloxifene trials. Dr. Carlson concluded that if the MORE findings had truly established that Evista reduces the risk of breast cancer to the degree claimed by Eli Lilly, one would have expected at least a trend in the same direction, if not a statistically significant difference, in the nine pooled studies of some 3,000 patients. No such trend is evident in the data. Tr. at 402-11 (Carlson).

***25** 83. With respect to the MORE study itself, Dr. Carlson identified several flaws, both in the design of the protocol and the analysis of the data. These flaws include the fact that MORE was designed primarily as an osteoporosis study and breast cancer appeared among several other safety-related issues in the seventh secondary endpoint of the study. In addition, the MORE protocol did not articulate a prospectively defined method for collecting and analyzing the breast cancer data in particular. Tr. at 411-14, 452-54 (Carlson). As Eli Lilly acknowledged, the statistical analysis contained in the MORE protocol was a general one specified for all of the safety endpoints in the trial. Tr. at 733 (Cummings); Tr. at 937, 941 (Eckert).

84. Dr. Carlson also explained that in a properly designed breast cancer trial such as the BCPT or STAR, it is crucial to recruit patients with a high risk of breast cancer to ensure a sufficient number of overall breast cancer events. Without an adequate number of cases, he opined, one cannot rule out the possibility that the results are due to chance. To that end, Dr. Carlson observed that a properly designed breast cancer study should assess patients for breast cancer risk prior to entry in the study using the GAIL risk assessment model, and patients should be equally randomized between the two arms of the study with respect to the full array of breast cancer risk factors. MORE failed to follow this procedure. Tr. at 415-19, 455-57, 467-68 (Carlson).

85. Dr. Carlson also identified diagnostic flaws in the protocol that cast doubt on the MORE breast cancer results. Tr. at 650-51, 732 (Cummings); *see also* Tr. at 111-22 (Dere). Finally, Dr. Carlson observed that women in the MORE study were permitted to take estrogen, which many believe increases the risk of breast cancer and may thus have confounded the results. Tr. at 419-27 (Carlson).

86. Dr. Jerry Lewis, formerly Chief of the Hematology and Oncology Division at the

University of California, Davis, and now Zeneca's Senior Medical Director for Oncology, also testified. Dr. Lewis has taught and practiced in the area of clinical oncology and also has extensive experience in the design and analysis of clinical drug trials. Tr. at 290-95 (Lewis); Pl.'s Exh. 77.

87. Dr. Lewis testified convincingly to the same list of criticisms as Dr. Carlson. Tr. at 334-46 (Lewis). He specifically noted that the study population in the MORE trial were women with osteoporosis, who tend to be at low risk for breast cancer. Tr. at 337-38 (Lewis). He also opined that Evista has "not been proven to be efficacious in reducing the incidence of breast cancer."Tr. at 328 (Lewis).

88. Finally, Zeneca offered the expert testimony of Dr. Mark Scott, a biostatistician with extensive experience in the design and analysis of clinical drug trials. Dr. Scott responded to Eli Lilly's argument that the many flaws in the MORE trial may be overlooked because the breast cancer results in MORE were statistically significant at a level of p =.000005. A p value of less than .05 typically is required for a finding of statistical significance in a clinical trial.[FN7]

FN7. Under typical circumstances, where the variable in question is the primary endpoint of the study, a p value of .05 means that the odds are one in 20 that the result in question is due to chance. On its face, a p value of .000005 means that the odds are five in one million that the results in question are due to chance.

***26** 89. Dr. Scott explained that because breast cancer risk reduction was not the primary endpoint of the MORE trial, and there was no pre-specified statistical plan for analyzing breast cancer data, it is inappropriate to use a p value of .05 as a benchmark to assess the statistical significance of the MORE breast cancer data. Rather, to ensure that the results in question were not due to chance, Dr. Scott opined that the appropriate p value should be adjusted to take into account the fact that breast cancer risk reduction was a secondary endpoint and just one of hundreds of statistical tests performed in the MORE trial. Tr. at 1143-45 (Scott).

90. Dr. Scott made that adjustment, using the well-established formula, acknowledged by Eli Lilly's witnesses, Tr. at 645 (Cummings), of dividing the p value of .05 by the number of tests conducted. According to the lead MORE investigator, Eli Lilly's expert Dr. Steven Cummings, 400 safety tests alone were conducted in MORE. Tr. at 646 (Cummings). Using that number, which did not even take into account the non-safety statistical analyses performed on the MORE data, Dr. Scott concluded that the appropriate p value to determine statistical significance was .000125. Tr. at 1144-45 (Scott).

91. Although the MORE trial's breast cancer results still achieved statistical significance using that figure, Dr. Scott's testimony illustrated the significance of the fact that the MORE trial had relatively few cases of breast cancer. As previously noted, in MORE there were 40 total cases of invasive breast cancer; this compares with 264 cases in the BCPT. Tr. at 322-23 (Lewis). Dr. Scott explained that, given the low number of overall breast cancer cases reported to date in the MORE trial, the addition of only five more cases on the raloxifene arm of the study-without a corresponding increase on the placebo arm-would render the result on which Eli Lilly now relies statistically insignificant. Tr. at 1145 (Scott). Dr. Scott testified to a number of hypothetical scenarios under which those five additional cancers on the raloxifene arm could occur. Tr. at 1146-48 (Scott).

92. Dr. Scott's conclusion is that the MORE data " are intriguing but they are not the stuff of proof."Tr. at 1167 (Scott).

93. Under these circumstances, the Court credits Dr. Scott's testimony that, because of the large number of analyses performed by Eli Lilly on the MORE data and the small overall number of breast cancer cases observed in the trial, the p value in the MORE study is insufficient to show that the MORE study proves that raloxifene reduces the risk of breast cancer.

F. Eli Lilly's rebuttal

94. Eli Lilly maintains that Evista has been proven to reduce the risk of breast cancer. In support of its

position, Eli Lilly cites (i) its own interpretation of what the FDA has communicated to Eli Lilly with respect to the MORE data, (ii) the testimony of three witnesses, all of whom are involved with the MORE study, and (iii) the peer-reviewed article about the MORE results recently published in JAMA. As set forth below, these materials fail to rebut Zeneca's showing on the merits.

1. *The dialogue between Eli Lilly and FDA*

***27** 95. First, Eli Lilly maintains that the FDA has declined to approve a breast cancer risk reduction claim on the basis of the MORE data not because it considered the MORE study to be flawed, but merely because the FDA requires two well-controlled clinical trials before approving a drug as safe and effective. In light of the FDA correspondence described above, Eli Lilly's position is not tenable. The approval of a risk reduction indication for tamoxifen on the basis of the BCPT and supporting evidence makes clear that FDA will approve drugs on the basis of one large-scale clinical study with supporting evidence. Tr. at 315-16 (Lewis); Tr. at 1151 (Scott). Indeed, Congress has made clear, and the FDA has acknowledged, that the FDA may base a finding of efficacy on one adequate and well-controlled clinical investigation along with confirmatory evidence. *See*21 U.S.C. § 355(d); *see also Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products ("Guidance for Industry"),* U.S. Dep't of Health & Human Services, Food & Drug Administration, May 1998, at 12-13.

96. Eli Lilly also contends that the statement the FDA required it to put on the label-"[t]he effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established"-is fdA'S way of communicating that Evista has been proven efficacious but is not yet indicated for breast cancer risk reduction. Tr. at 216, 850 (Torres); Tr. at 917 (Eckert); 1004-05 (Harenberg). This argument ignores the plain meaning of the word "established" and is also at odds with some of the testimony of Eli Lilly's own witnesses. For example, Dr. Cummings conceded that the statement means, at a minimum, that the efficacy of Evista in reducing the risk of breast cancer has not yet been proven to the satisfaction of the FDA. Tr. at 631-32, 638-39 (Cummings). Moreover, Eli Lilly's interpretation is contrary to the plain meaning of the FDA documents. Eli Lilly's witnesses simply disagree with the FDA or with the statement. Lippman Dep. Tr. at 158; Tr. at 1097-98 (Dere).[FN8]

FN8. One Eli Lilly executive, who has attended meetings of Eli Lilly's Raloxifene Advisory Board, which is composed of Eli Lilly and non-Eli Lilly scientists, conceded at his deposition that he understood Eli Lilly cannot make a breast cancer risk reduction claim for the drug because "[i]t's not a proven claim."Tr. at 238 (Harenberg). The executive's attempts at trial to explain away his prior deposition testimony were unconvincing, especially since he agreed at trial that Eli Lilly cannot make claims that Evista prevents breast cancer. Tr. at 1004-08 (Harenberg).

97. Eli Lilly also suggests that the dialogue with the FDA is still ongoing and that the findings and opinions set forth in the January 1999 minutes with respect to MORE, and the May 1999 minutes with respect to MORE and CORE, do not reflect the agency's last word on the subject or are an incorrect recitation of the FDA's position. This argument is contradicted by the FDA's repeated statements over a two-year period. And whether or not the dialogue is ongoing, the FDA has made abundantly clear that MORE-either alone or in conjunction with CORE-does not and cannot prove that Evista reduces the risk of breast cancer. That is why Evista's label states that the effectiveness of Evista in reducing the risk of breast cancer has not yet been established and why the FDA will require Eli Lilly to rely on data generated by STAR, RUTH or both in any application for a breast cancer risk reduction indication for Evista.

2. *Eli Lilly's expert witnesses*

***28** 98. Eli Lilly also offered the testimony of three